# ENHANCED TRANSPORT USING MEMBRANE DISRUPTIVE AGENTS

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**Inventor(s):**
**Applicant(s):**
**Classification:**
**- international:** ***A61K31/7105; A61K31/711; A61K41/00; A61K47/32; A61K47/42; A61K47/48; A61K9/00;*** **A61K31/7105; A61K31/711; A61K41/00; A61K47/32; A61K47/42; A61K47/48; A61K9/00;** (IPC1-7): A61K31/7105; A61K31/711; A61K47/32; A61K47/42; A61K47/48; A61K9/00
**- European:** A61K41/00M, A61K41/00T; A61K47/48T2
**Application number:** JP20000527278T 19990105
**Priority number(s):** US19980070411P 19980105; WO1999US00122 19990105

**Also published as:**
WO9934831 (A1)
EP1044021 (A1)
EP1044021 (B1)
EP2138191 (A1)
CA2317549 (A1)
more >>

Abstract not available for JP 2002500201 (T)
Abstract of corresponding document: **WO 9934831 (A1)**

Compositions and methods for transport or release of therapeutic and diagnostic agents or metabolites or other analytes from cells, compartments within cells, or through cell layers or barriers are described. The compositions include a membrane barrier transport enhancing agent and are usually administered in combination with an enhancer and/or exposure to stimuli to effect disruption or altered permeability, transport or release. In a preferred embodiment, the compositions include compounds which disrupt endosomal membranes in response to the low pH in the endosomes but which are relatively inactive toward cell membranes, coupled directly or indirectly to a therapeutic or diagnostic agent. Other disruptive agents can also be used, responsive to stimuli and/or enhancers other than pH, such as light, electrical stimuli, electromagnetic stimuli, ultrasound, temperature, or combinations thereof. The compounds can be coupled by ionic, covalent or H bonds to an agent to be delivered or to a ligand which forms a complex with the agent to be delivered. Agents to be delivered can be therapeutic and/or diagnostic agents. Treatments which enhance delivery such as ultrasound, iontopheresis, and/or electropheresis can also be used with the disrupting agents.

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特表2002－500201
（P2002－500201A）
(43)公表日　平成14年１月８日(2002.1.8)

| (51)Int.Cl.[7] | 識別記号 | ＦＩ | ﾃｰﾏｺｰﾄﾞ(参考) |
|---|---|---|---|
| Ａ６１Ｋ　47/32 | | Ａ６１Ｋ　47/32 | ４Ｃ０７６ |
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| 31/7105 | | 31/7105 | |
| 31/711 | | 31/711 | |
| 47/42 | | 47/42 | |

審査請求　未請求　予備審査請求　有　（全 62 頁）　最終頁に続く

(21)出願番号　特願2000－527278(P2000－527278)
(86)(22)出願日　平成11年１月５日(1999.1.5)
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(86)国際出願番号　ＰＣＴ／ＵＳ９９／００１２２
(87)国際公開番号　ＷＯ９９／３４８３１
(87)国際公開日　平成11年７月15日(1999.7.15)
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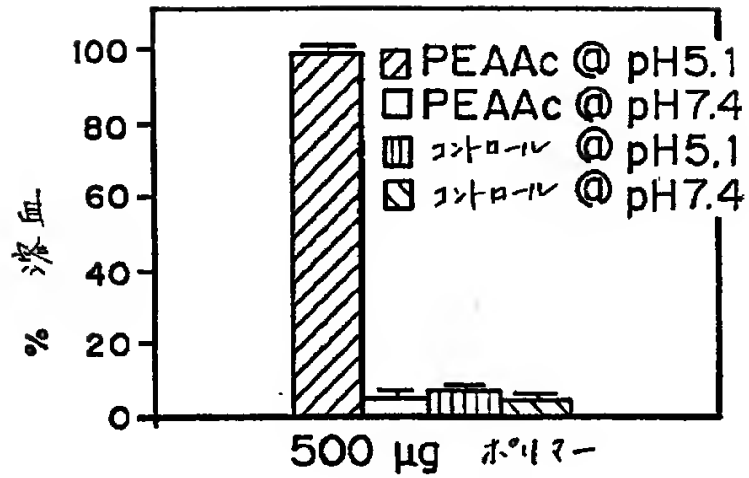
(33)優先権主張国　米国（ＵＳ）
(81)指定国　ＥＰ(ＡＴ，ＢＥ，ＣＨ，ＣＹ，ＤＥ，ＤＫ，ＥＳ，ＦＩ，ＦＲ，ＧＢ，ＧＲ，ＩＥ，ＩＴ，ＬＵ，ＭＣ，ＮＬ，ＰＴ，ＳＥ)，ＡＵ，ＣＡ，ＪＰ

(71)出願人　ユニバーシティ　オブ　ワシントン
アメリカ合衆国　ワシントン州　シアトル、ユニバーシティ、ウェイ、ノース、イースト、4014
(71)出願人　ユニバーシティ　オブ　マサチューセッツ
アメリカ合衆国　マサチューセッツ　02108，　ボストン，　トレモント　ストリート　18，　スイート　800
(72)発明者　ホフマン，　アラン　エス．
アメリカ合衆国　ワシントン　98105，　シアトル，　エヌ．イー．，　ウエスト　ローレル　ドライブ　4528
(74)代理人　弁理士　山本　秀策

最終頁に続く

(54)【発明の名称】　膜破壊剤を使用する増強された輸送

(57)【要約】
治療剤および診断剤、または代謝産物、または他の分析物の、細胞からの、細胞内区画からの、あるいは細胞層または細胞障壁を通っての、輸送あるいは放出のための組成物および方法が記載される。これらの組成物は、膜障壁輸送増強剤を含み、そして通常、増強因子および／あるいは、破壊または透過性の変化、輸送の変化、もしくは放出の変化をもたらす刺激への曝露と組合せて投与される。好ましい実施態様において、これらの組成物は、エンドソームの低ｐＨに応答してエンドソーム膜を破壊するが、細胞膜に対しては比較的不活性である化合物を含み、治療剤または診断剤と、直接あるいは間接的に結合される。ｐＨ以外の刺激および／または増強因子（例えば、光、電気的刺激、電磁気的刺激、超音波、温度またはそれらの組合せ）に応答性である他の破壊剤もまた使用され得る。これらの化合物は、イオン結合、共有結合、または水素結合により、送達される薬剤あるいは送達される薬剤と複合体を形成するリガンドに結合され得る。送達される薬剤は、治療剤および／または診断剤であり得る。超音波、イオン泳動、および／または電気泳動のような、送達を増強する処置もまた、破壊剤と共に使用され得る。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80
60
40
20
0
% 溶血
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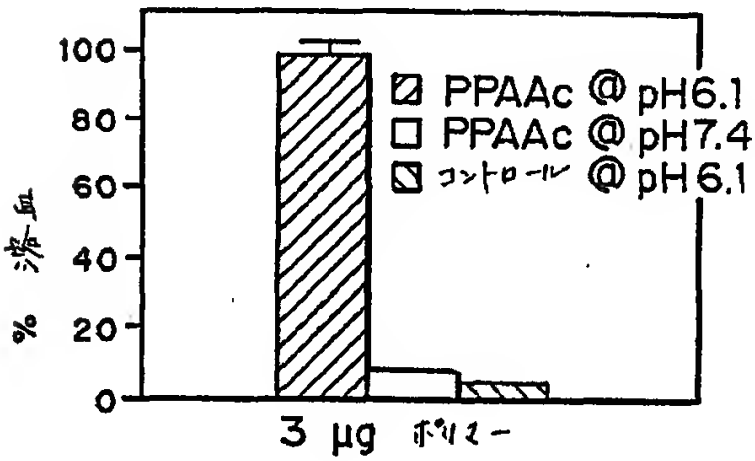
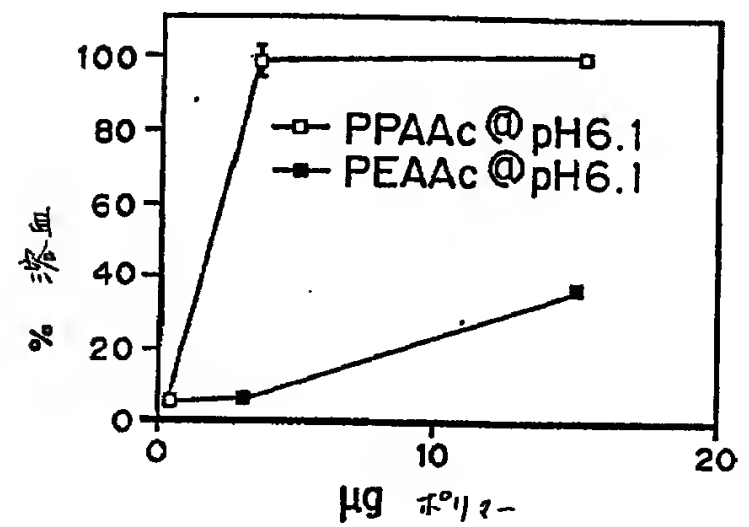
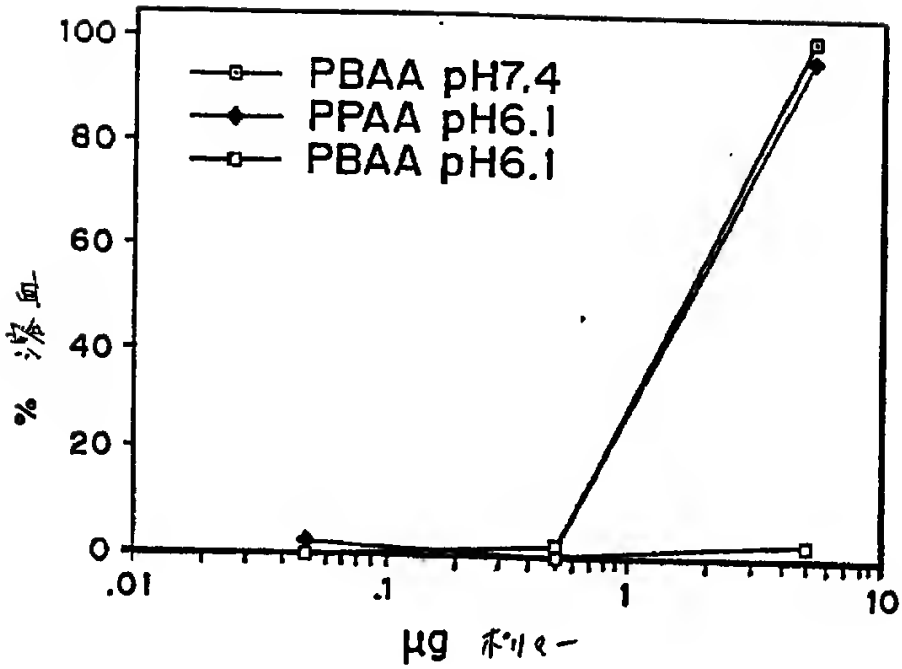
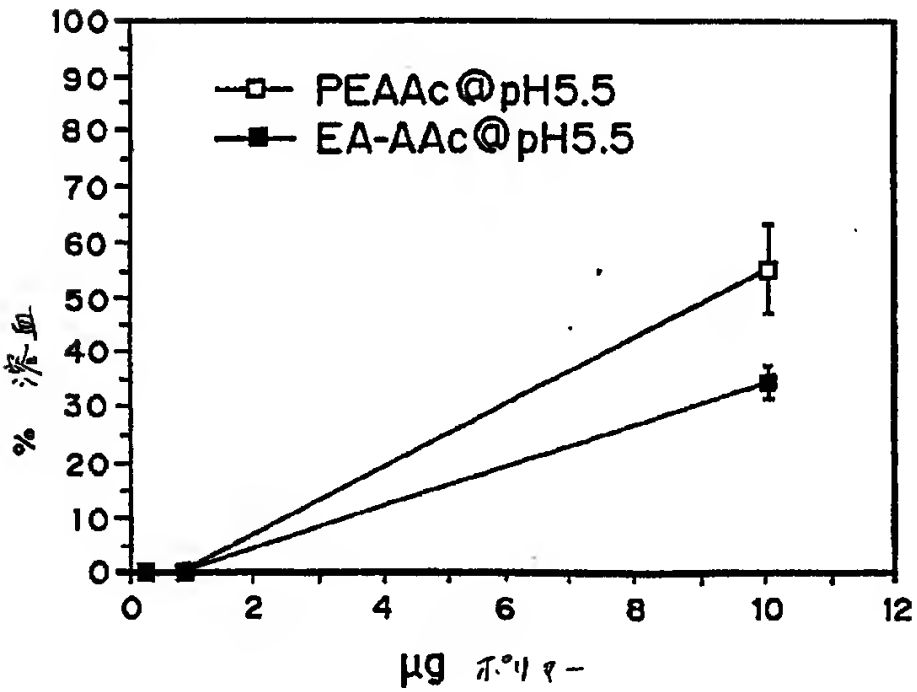
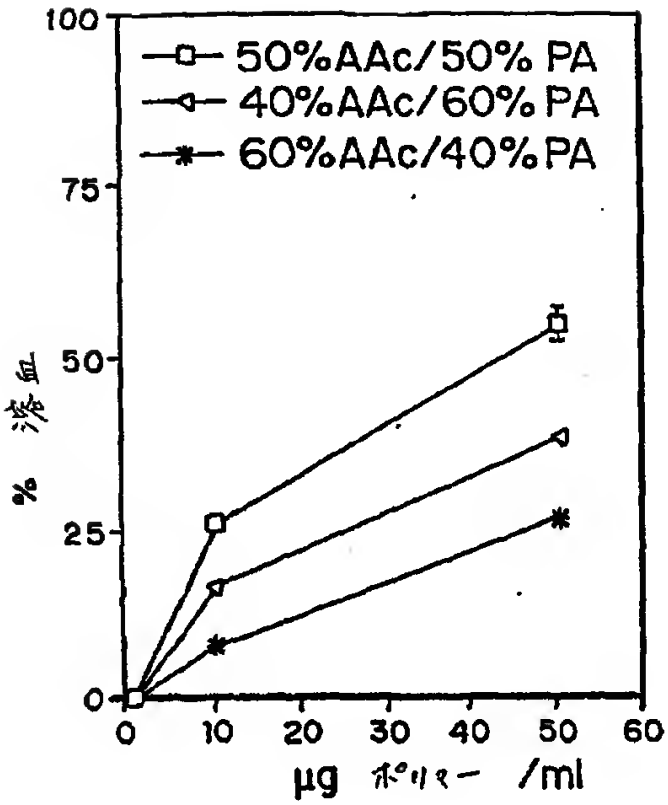
PEAAc @ pH7.4
コントロール @ pH5.1
コントロール @ pH7.4
500 μg ポリマー

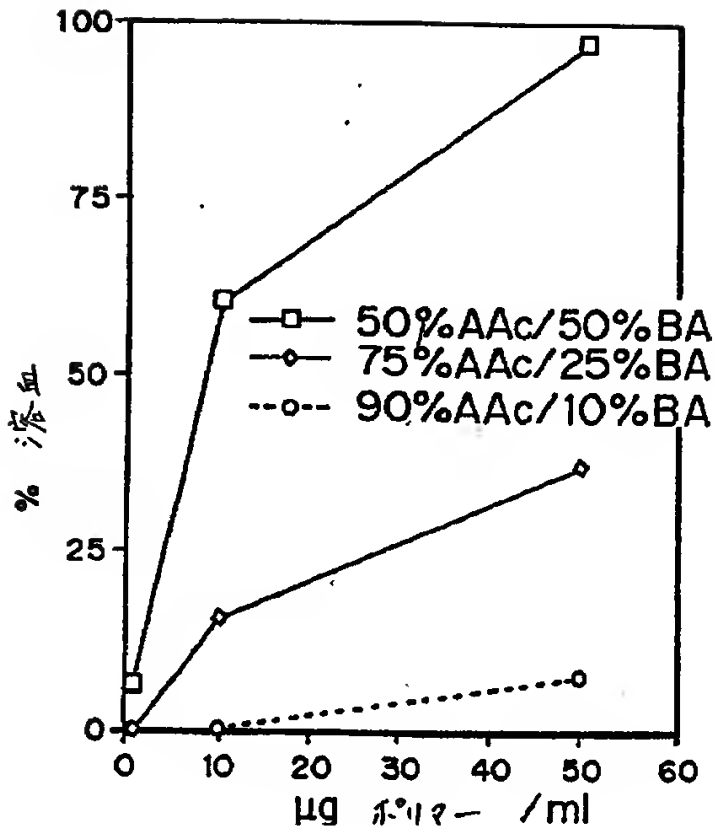

100
80
60
40
20
0
% 溶血
PPAAc @ pH6.1
PPAAc @ pH7.4
コントロール @ pH6.1
3 μg ポリマー

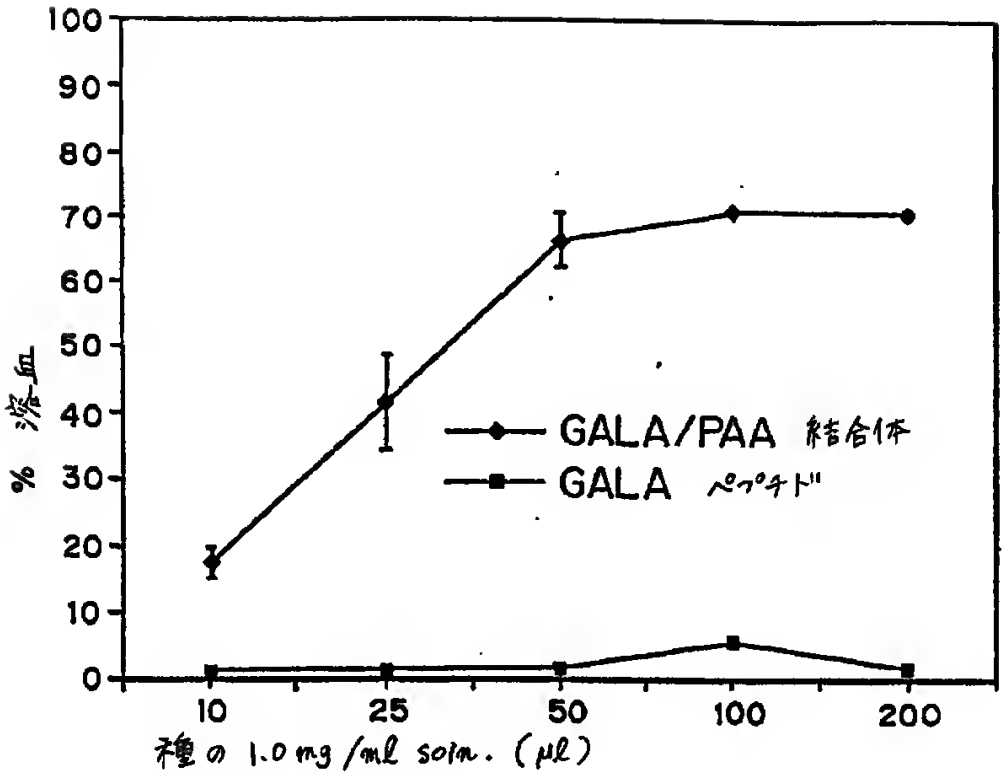

100
80
60
40
20
0
% 溶血
PPAAc @ pH6.1
PEAAc @ pH6.1
0
10
20
μg ポリマー

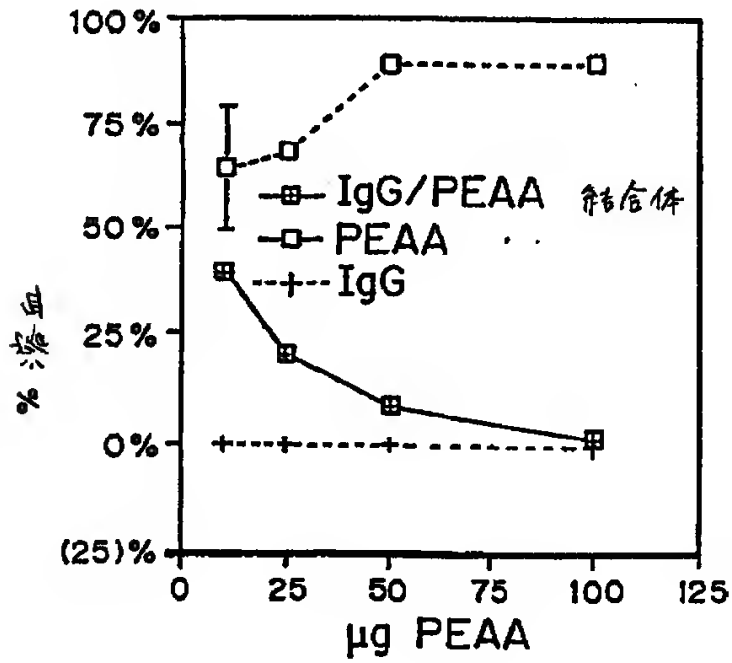

PBAA pH7.4
PPAA pH6.1
PBAA pH6.1
% 溶血
100
80
60
40
20
0
.01
.1
1
10
μg ポリマー

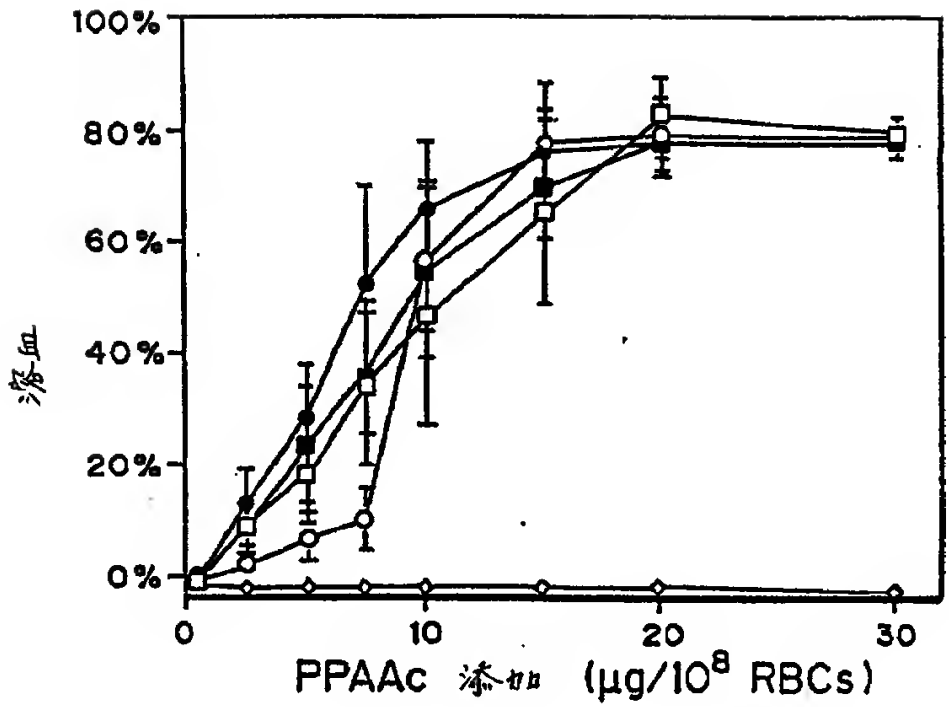

PEAAc@pH5.5
EA-AAc@pH5.5
% 溶血
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
μg ポリマー

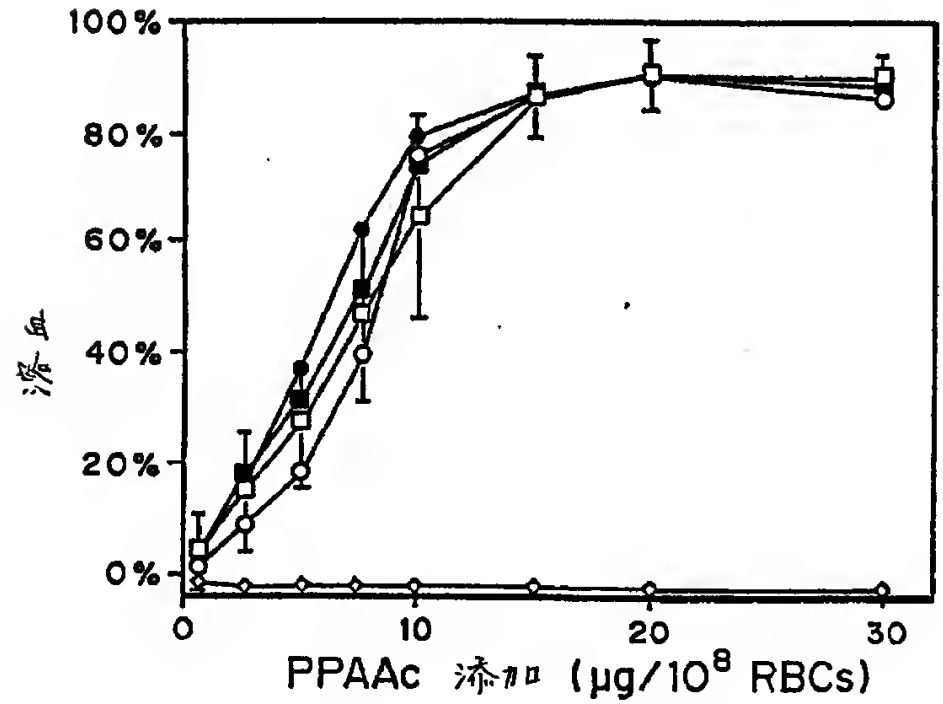

100
75
50
25
0
% 溶血
50%AAc/50% PA
40%AAc/60% PA
60%AAc/40% PA
0
10
20
30
40
50
60
μg ポリマー /ml

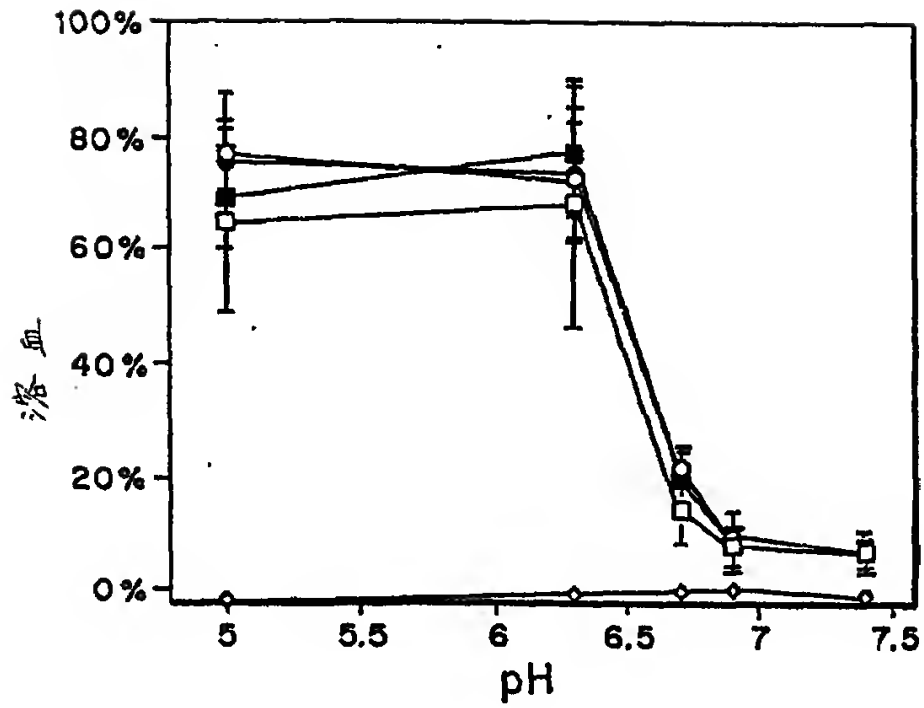

100
75
50
25
0
% 溶血
0
10
20
30
40
50
60
μg ポリマー /ml
50%AAc/50%BA
75%AAc/25%BA
90%AAc/10%BA

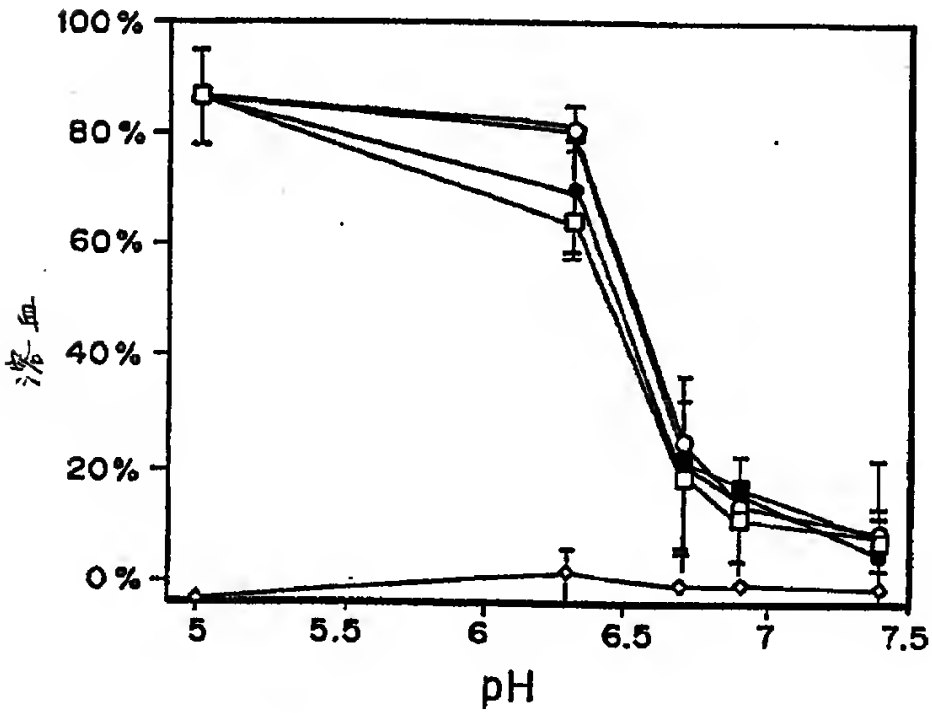

100
90
80
70
60
50
40
30
20
10
0
% 溶血
GALA/PAA 結合体
GALA ペプチド
10
25
50
100
200
種の 1.0 mg/ml soln. (μl)

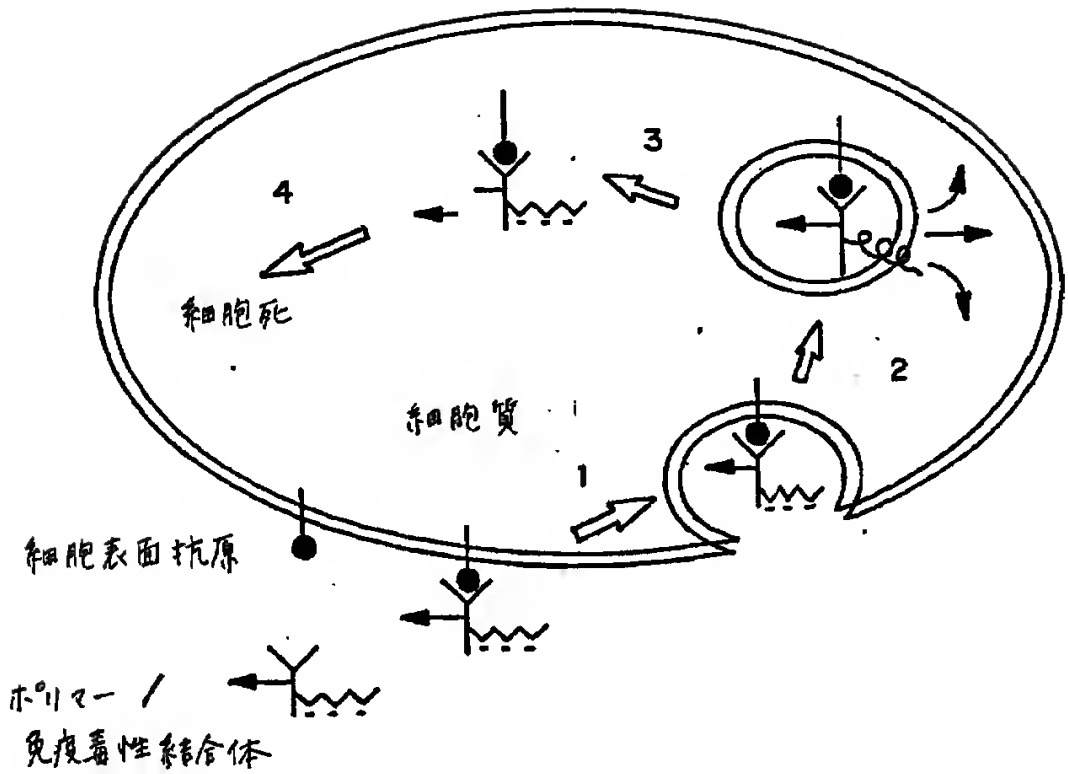

100%
75%
50%
25%
0%
(25)%
% 溶血
IgG/PEAA 結合体
PEAA
IgG
0
25
50
75
100
125
μg PEAA

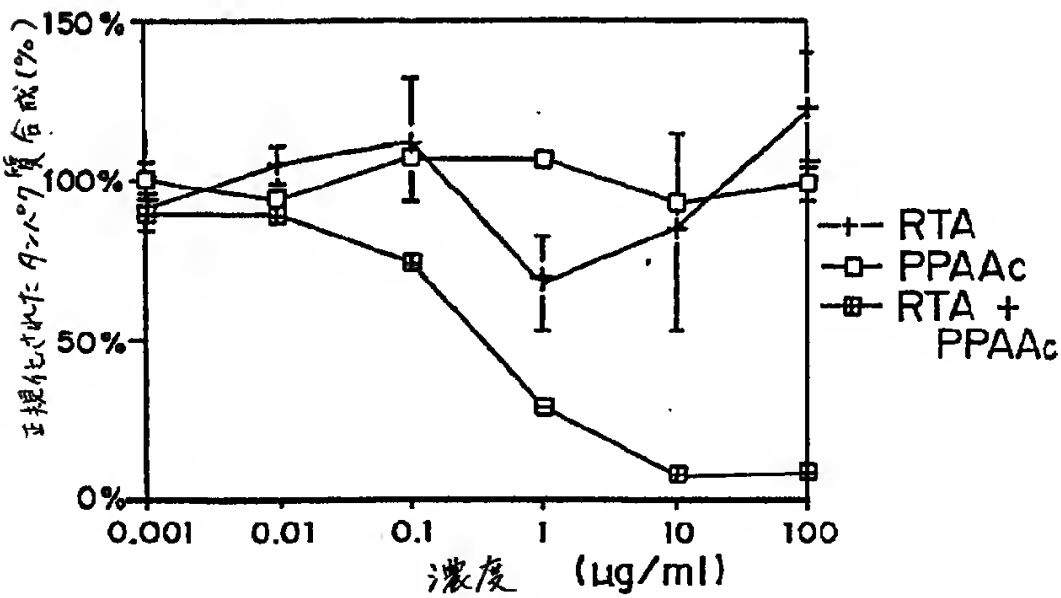

100%
80%
60%
40%
20%
0%
溶血
0
10
20
30
PPAAc 添加 (μg/10^8 RBCs)

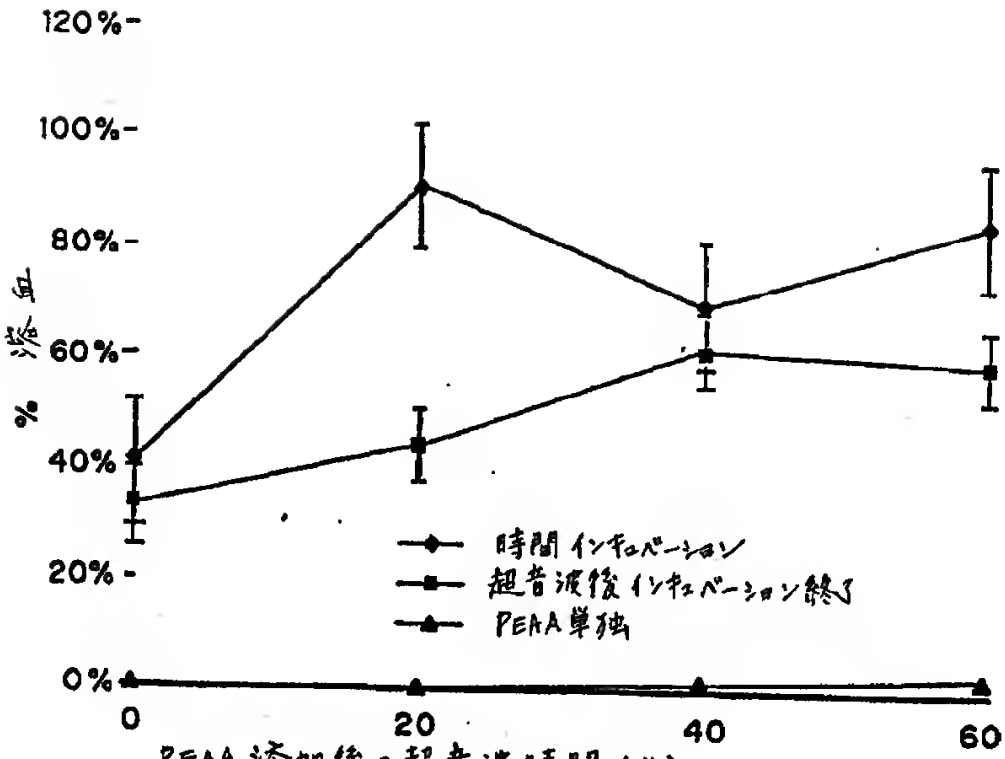

100%
80%
60%
40%
20%
0%
溶血
0
10
20
30
PPAAc 添加 (μg/10^8 RBCs)

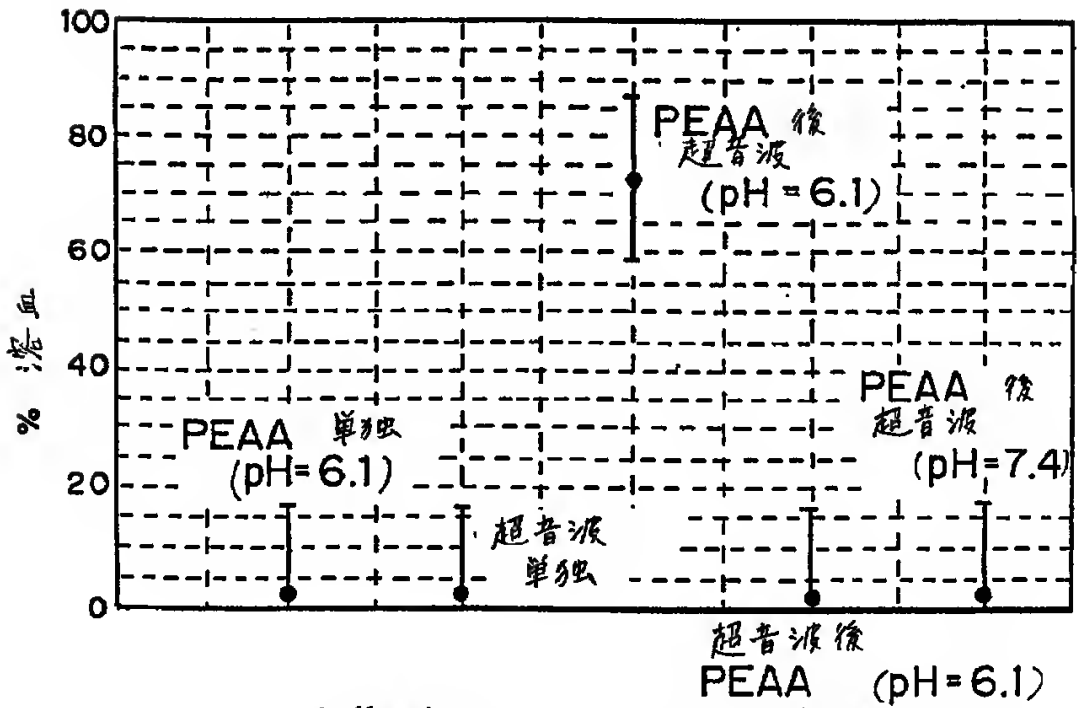

100%
80%
60%
40%
20%
0%
溶血
5
5.5
6
6.5
7
7.5
pH


100%
80%
60%
40%
20%
0%
溶血
5
5.5
6
6.5
7
7.5
pH


3
4
細胞死
2
細胞質
1
細胞表面抗原
ポリマー / 免疫毒性結合体


150%
100%
50%
0%
0.001
0.01
0.1
1
10
100
濃度 (μg/ml)
RTA
PPAAc
RTA + PPAAc




タンパク質の高次構造が US/PEAA 相乗作用を決定する

# INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 99/00122

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/32 A61K47/42 A61K47/48 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ' | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 97 09068 A (UNIV WASHINGTON)<br>13 March 1997 | 1-8,12 |
| A | see page 4, line 11-20<br>see page 10, line 19 - page 22, line 14<br>see page 53, line 15 - page 54, line 4<br>see claims<br>see figure 8 | 15 |
| | --- | |
| X | WO 96 40958 A (BAYLOR COLLEGE MEDICINE)<br>19 December 1996 | 1,3,5,6,<br>8,11,12 |
| A | see page 7, line 7-24<br>see page 8, line 25-34<br>see page 9, line 34 - page 10, line 15<br>see page 13, line 5-13<br>see page 15, line 10-15<br>see page 19, line 21 - page 20, line 7<br>see page 66, line 18-22<br>see claims | 15-20 |
| | ---<br>-/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

' Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 19 April 1999 | 28/04/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax. (+31-70) 340-3016 | La Gaetana, R |

2

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/US 99/00122

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 5 547 932 A (CURIEL DAVID T ET AL)<br>20 August 1996 | 1,3,5,6,<br>8,9,11,<br>12 |
| A | see column 4, line 63 - column 5, line 29<br>see column 9, line 51-62<br>see column 15, line 36-51<br>see claims<br>see example 12 | 15-20 |
| X | PLANK C ET AL: "THE INFLUENCE OF ENDOSOME-DISRUPTIVE PEPTIDES ON GENE TRANSFER USING SYNTHETIC VIRUS-LIKE GENE TRANSFER SYSTEMS"<br>JOURNAL OF BIOLOGICAL CHEMISTRY,<br>vol. 269, no. 17, 29 April 1994, pages 12918-12924, XP000615488<br>cited in the application<br>see abstract<br>see page 1291B, column 1<br>see Disussion | 1,3,5,6,<br>11 |
| A | WO 97 04832 A (MASSACHUSETTS INST TECHNOLOGY) 13 February 1997<br>see page 6, line 1 - page 7, line 2<br>see page 11, line 10 - page 12, line 7<br>see page 12, line 34 - page 13, line 7<br>see page 23, line 21 - page 24, line 5<br>see claims 1,2,13,22-24 | 1-20 |
| A | US 4 657 543 A (LANGER ROBERT S ET AL)<br>14 April 1987<br>see column 1, line 45-64<br>see column 4, line 41-61<br>see claims | 1-20 |
| X | HUGHES JA, ARONSHN AI, AVRUTSKAYA AV, JULIANO RL: "Evaluation of adjuvants that enhance the effectiveness of antisense oligodeoxynucleotides"<br>PHARMACOLOGICAL RESEARCH,<br>vol. 13, no. 3, March 1996, pages 404-10, XP002100198<br>cited in the application<br>see abstract<br>see Discussion | 1,3,5,6,<br>12,13 |
| A | KOST J, LANGER R: "Responsive poymer systems for controlled delivery of therapeutics"<br>TRENDS INBIOTECHNOLOGY,<br>vol. 10, no. 4, April 1992, pages 127-131, XP002100199<br>see the whole document | 1-20 |

2

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US 99/ 00122

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 99/00122

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO 9709068 A | 13-03-1997 | AU | 7011096 A | 27-03-1997 |
| | | CA | 2230557 A | 13-03-1997 |
| | | EP | 0851768 A | 08-07-1998 |
| WO 9640958 A | 19-12-1996 | AU | 5714296 A | 30-12-1996 |
| | | CA | 2222550 A | 19-12-1996 |
| | | EP | 0832269 A | 01-04-1998 |
| US 5547932 A | 20-08-1996 | AU | 671084 B | 15-08-1996 |
| | | AU | 2652692 A | 03-05-1993 |
| | | BG | 98718 A | 28-02-1995 |
| | | BR | 9206559 A | 08-11-1994 |
| | | CA | 2118816 A | 31-03-1993 |
| | | CZ | 9400746 A | 17-05-1995 |
| | | WO | 9307283 A | 15-04-1993 |
| | | EP | 0545016 A | 09-06-1993 |
| | | EP | 0607206 A | 27-07-1994 |
| | | FI | 941474 A | 30-03-1994 |
| | | HU | 71312 A | 28-11-1995 |
| | | HU | 9500694 A | 29-01-1996 |
| | | JP | 10506001 T | 16-06-1998 |
| | | MX | 9205543 A | 01-05-1993 |
| | | NO | 941154 A | 29-03-1994 |
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